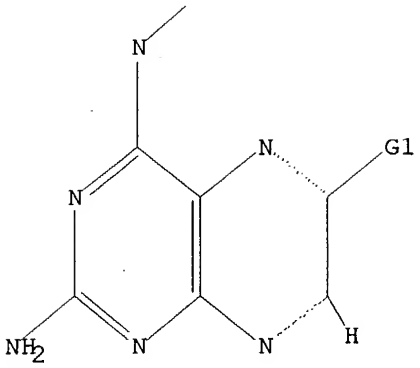


G1 C,Cy

Structure attributes must be viewed using STN Express query preparation.

=> s l6 sss full
FULL SEARCH INITIATED 19:05:01 FILE 'REGISTRY'
FULL SCREEN SEARCH COMPLETED - 869 TO ITERATE

100.0% PROCESSED 869 ITERATIONS 42 ANSWERS
SEARCH TIME: 00.00.01

L7 42 SEA SSS FUL L6

=> file caplus

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	155.42	615.05

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)	SINCE FILE ENTRY	TOTAL SESSION
CA SUBSCRIBER PRICE	0.00	-20.79

FILE 'CAPLUS' ENTERED AT 19:05:06 ON 06 MAY 2004
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.

FILE COVERS 1907 - 6 May 2004 VOL 140 ISS 19
FILE LAST UPDATED: 5 May 2004 (20040505/ED)

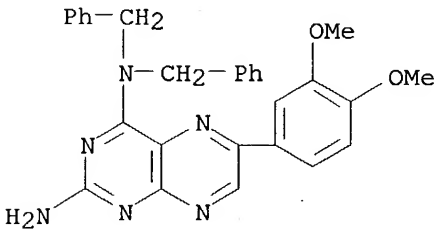
This file contains CAS Registry Numbers for easy and accurate substance identification.

=> s l7
L8 10 L7

=> d l8 1-10 ibib abs hitstr

L8 ANSWER 1 OF 10 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2002:392358 CAPLUS
DOCUMENT NUMBER: 137:119060
TITLE: Structural Requirements for Inhibition of the Neuronal Nitric Oxide Synthase (NOS-I): 3D-QSAR Analysis of 4-Oxo- and 4-Amino-Pteridine-Based Inhibitors
AUTHOR(S): Matter, Hans; Kotsonis, Peter; Klingler, Otmar; Strobel, Hartmut; Froehlich, Lothar G.; Frey, Armin; Pfleiderer, Wolfgang; Schmidt, Harald H. H. W.
CORPORATE SOURCE: Molecular Modeling, Aventis Pharma, Frankfurt am Main, 65926, Germany
SOURCE: Journal of Medicinal Chemistry (2002), 45(14), 2923-2941
CODEN: JMCMAR; ISSN: 0022-2623
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The family of homodimeric nitric oxide synthases (NOS I-III) catalyzes the generation of the cellular messenger nitric oxide (NO) by oxidation of the substrate L-arginine. The rational design of specific NOS inhibitors is of therapeutic interest in regulating pathol. NO levels associated with sepsis, inflammatory, and neurodegenerative diseases. The cofactor (6R)-5,6,7,8-tetrahydrobiopterin (H4Bip) maximally activates all NOSs and stabilizes enzyme quaternary structure by promoting and stabilizing dimerization. Here, we describe the synthesis and three-dimensional (3D) quant. structure-activity relationship (QSAR) anal. of 65 novel 4-amino- and 4-oxo-pteridines (antipterins) as inhibitors targeting the H4Bip binding site of the neuronal NOS isoform (NOS-I). The exptl. binding modes for two inhibitors complexed with the related endothelial NO synthase (NOS-III) reveal requirements of biol. affinity and form the basis for ligand alignment. Different alignment rules were derived by building other compds. accordingly using manual superposition or a genetic algorithm for flexible superposition. Those alignments led to 3D-QSAR models (comparative mol. field anal. (CoMFA) and comparative mol. similarity index anal. (CoMSIA)), which were validated using leave-one-out cross-validation, multiple analyses with two and five randomly chosen cross-validation groups, perturbation of biol. activities by randomization or progressive scrambling, and external prediction. An iterative realignment procedure based on rigid field fit was used to improve the consistency of the resulting partial least squares models. This led to consistent and highly predictive 3D-QSAR models with good correlation coeffs. for both CoMFA and CoMSIA, which correspond to exptl. determined NOS-II and -III H4Bip binding site topologies as well as to the NOS-I homol. model binding site in terms of steric, electrostatic, and hydrophobic complementarity. These models provide clear guidelines and accurate activity predictions for novel NOS-I inhibitors.
IT **278800-01-4P 330575-46-7P 330575-47-8P 330575-48-9P**
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation and QSAR of 4-oxo- and 4-amino-pteridine-based neuronal NOS inhibitors)
RN 278800-01-4 CAPLUS

CN 2,4-Pteridinediamine, 6-(3,4-dimethoxyphenyl)-N4,N4-bis(phenylmethyl)-
(9CI) (CA INDEX NAME)



RN 330575-46-7 CAPLUS
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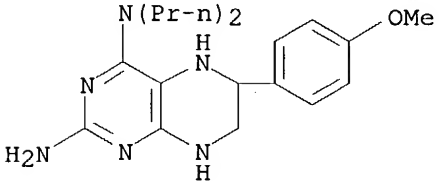
dipropyl-, dihydrochloride (9CI) (CA INDEX NAME)



●2 HCl

RN 330575-47-8 CAPLUS
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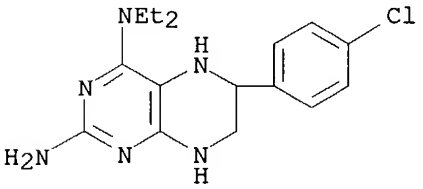
, dihydrochloride (9CI) (CA INDEX NAME)



●2 HCl

RN 330575-48-9 CAPLUS
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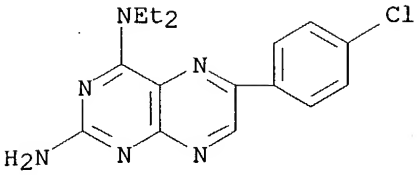
tetrahydro-, dihydrochloride (9CI) (CA INDEX NAME)



RN 278800-00-3 CAPLUS
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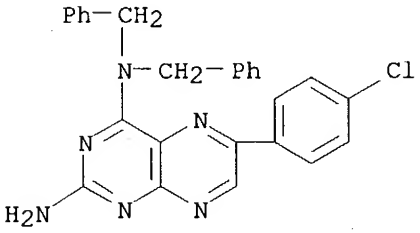
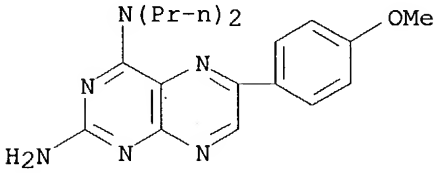


RN 278800-04-7 CAPLUS
CN 2,4-Pteridinediamine, 6-(4-methoxyphenyl)-N4,N4-dipropyl- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 111 THERE ARE 111 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

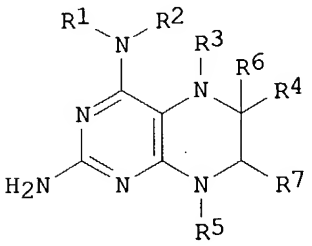
L8 ANSWER 2 OF 10 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2001:228889 CAPLUS
DOCUMENT NUMBER: 134:237499
TITLE: Preparation of N-substituted-4-aminopteridines as NO synthase inhibitors for use as pharmaceuticals
INVENTOR(S): Pfleiderer, Wolfgang; Schmidt, Harald; Froehlich, Lothar; Kotsonis, Peter; Taghavi-Moghadam, Shahriyar
PATENT ASSIGNEE(S): Vasopharm Biotech G.m.b.H. & Co. K.-G., Germany
SOURCE: PCT Int. Appl., 43 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001021619	A1	20010329	WO 2000-EP8833	20000911

present case

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG
DE 19944767 A1 20010329 DE 1999-19944767 19990917
EP 1216246 A1 20020626 EP 2000-964154 20000911
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL
PRIORITY APPLN. INFO.: DE 1999-19944767 A 19990917
WO 2000-EP8833 W 20000911
OTHER SOURCE(S): MARPAT 134:237499

GI



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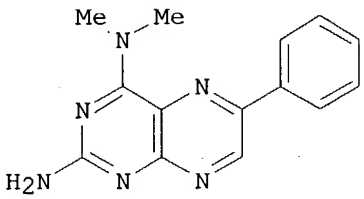


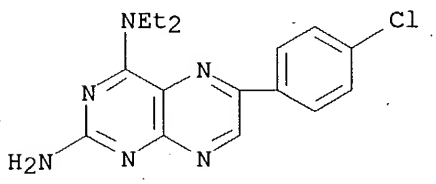
II

AB Pteridines, such as I [R1, R2 = H, alkyl, aryl, arylalkyl; R1R2 = nitrogen bound heterocyclyl, such as 1-piperidinyl or 4-morpholinyl; R4 = alkyl, alkenyl, alkynyl, cycloalkenyl, aryl, etc.; R3, R5 = acyl, aroyl, R6 = R7 = H, or R3R6 = R5R7 = bond;], were prepared for pharmaceutical use. Thus, pteridine II was prepared via cyclocondensation of N4,N4-dimethylpyrimidinetetramine dihydrochloride and phenylglyoxal monoxime. The prepared pteridines were tested for nitric oxide synthase inhibiting activity.

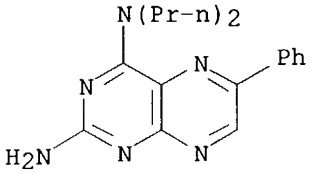
IT **278799-98-7P 278800-02-5P 278800-04-7P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(preparation of N-substituted-4-aminopteridines as NO synthase inhibitors for pharmaceutical use)

RN 278799-98-7 CAPLUS

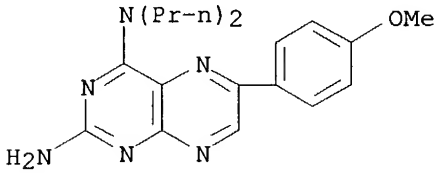
CN 2,4-Pteridinediamine, 6-(4-chlorophenyl)-N4,N4-diethyl- (9CI) (CA INDEX NAME)



RN 278800-02-5 CAPLUS
CN 2,4-Pteridinediamine, 6-phenyl-N4,N4-dipropyl- (9CI) (CA INDEX NAME)

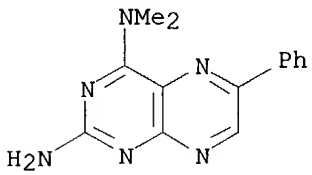


RN 278800-04-7 CAPLUS
CN 2,4-Pteridinediamine, 6-(4-methoxyphenyl)-N4,N4-dipropyl- (9CI) (CA INDEX NAME)

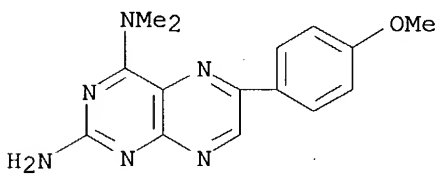


IT **247913-51-5P 247913-52-6P 247913-54-8P**
247913-55-9P 247913-56-0P 247913-57-1P
278799-96-5P 278799-99-8P 278800-00-3P
278800-01-4P 278800-03-6P 278800-05-8P
330575-31-0P 330575-45-6P 330575-46-7P
330575-47-8P 330575-48-9P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of N-substituted-4-aminopteridines as NO synthase inhibitors for pharmaceutical use)

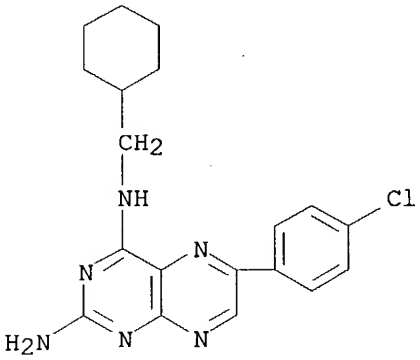
RN 247913-51-5 CAPLUS
CN 2,4-Pteridinediamine, N4,N4-dimethyl-6-phenyl- (9CI) (CA INDEX NAME)



RN 247913-52-6 CAPLUS
CN 2,4-Pteridinediamine, 6-(4-methoxyphenyl)-N4,N4-dimethyl- (9CI) (CA INDEX NAME)



CN 2,4-Pteridinediamine, 6-(4-chlorophenyl)-N4-(cyclohexylmethyl)- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 8 THERE ARE 8 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 3 OF 10 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2000:457070 CAPLUS
DOCUMENT NUMBER: 133:73895
TITLE: Preparation of pteridine derivatives for pharmaceutical use in the treatment of inflammatory diseases and autoimmune disorders
INVENTOR(S): Waer, Mark Joseph Albert; Herdewijn, Piet Andre Maurits Maria; Pfleiderer, Wolfgang Eugen
PATENT ASSIGNEE(S): K.U. Leuven Research & Development, Belg.
SOURCE: PCT Int. Appl., 56 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

Schmidt Fröhlich Krotsan Mergenthaler

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000039129	A1	20000706	WO 1999-EP10320	19991228
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
CA 2356380	AA	20000706	CA 1999-2356380	19991228
EP 1144412	A1	20011017	EP 1999-964663	19991228
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
JP 2002533464	T2	20021008	JP 2000-591040	19991228
US 2004077859	A1	20040422	US 2003-651604	20030829

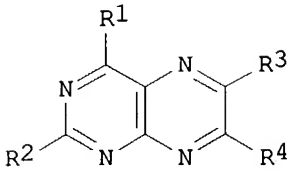
< 11/29/00

PRIORITY APPLN. INFO.: US 1998-113989P P 19981228 60/113,989
WO 1999-EP10320 W 19991228
US 2001-869468 B2 20011010

OTHER SOURCE(S): MARPAT 133:73895

09/869,468 ABN → 10/651,604

GI



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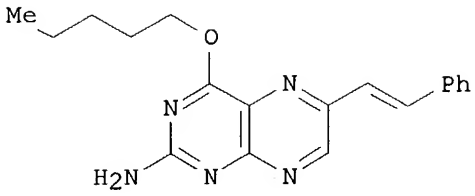


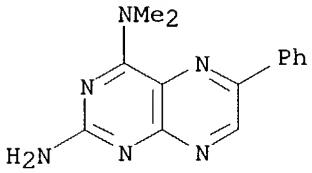
II

AB Pteridines, such as I [R1, R2 = NH2, NHOH, alkylamine, dialkylamine, alkyloxyamine, dialkyloxyamine, nitrogen containing heterocyclyl, etc.; R3 = halogen, alkoxy, alkyl, aryl, etc.; R4 = H, alkyl, alkoxy, aryl] were prepared for pharmaceutical use in the treatment of inflammatory diseases and autoimmune disorders. Thus, pteridine II was prepared in 72% yield by reaction of 6-chloro-4-(pentyloxy)-2-pteridinamine and styrene using palladium acetate, tri-o-tolylphosphine, cuprous iodide, and triethylamine in acetonitrile. The prepared pteridines were tested for immunosuppressive and anti-inflammatory activity.

IT **247913-51-5P 247913-52-6P 247913-54-8P**
247913-55-9P 247913-56-0P 247913-57-1P
278799-96-5P 278799-98-7P 278799-99-8P
278800-00-3P 278800-01-4P 278800-02-5P
278800-03-6P 278800-04-7P 278800-05-8P
278800-17-2P 278800-19-4P 278800-20-7P
278800-21-8P 278800-22-9P 278800-24-1P
278800-26-3P 278800-27-4P 278800-29-6P
278800-30-9P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of pteridine derivs. for pharmaceutical use in the treatment of inflammatory diseases and autoimmune disorders)

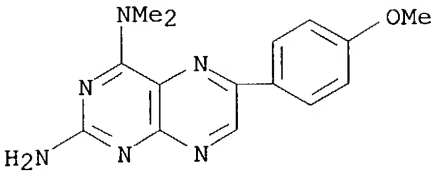
RN 247913-51-5 CAPLUS

CN 2,4-Pteridinediamine, N4,N4-dimethyl-6-phenyl- (9CI) (CA INDEX NAME)

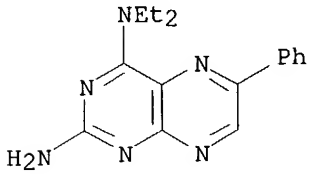


RN 247913-52-6 CAPLUS

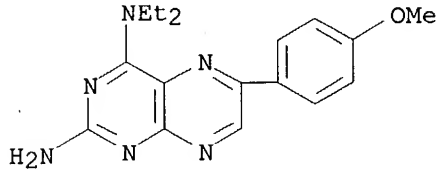
CN 2,4-Pteridinediamine, 6-(4-methoxyphenyl)-N4,N4-dimethyl- (9CI) (CA INDEX NAME)



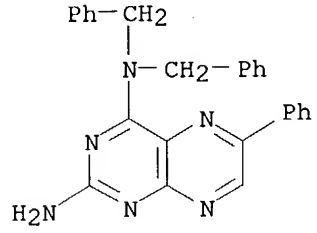
RN 247913-54-8 CAPLUS
CN 2,4-Pteridinediamine, N4,N4-diethyl-6-phenyl- (9CI) (CA INDEX NAME)



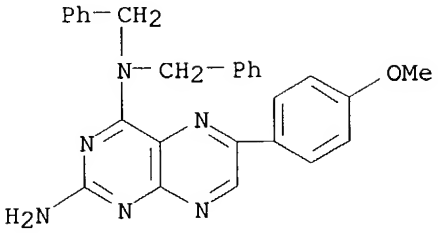
RN 247913-55-9 CAPLUS
CN 2,4-Pteridinediamine, N4,N4-diethyl-6-(4-methoxyphenyl)- (9CI) (CA INDEX NAME)



RN 247913-56-0 CAPLUS
CN 2,4-Pteridinediamine, 6-phenyl-N4,N4-bis(phenylmethyl)- (9CI) (CA INDEX NAME)



RN 247913-57-1 CAPLUS
CN 2,4-Pteridinediamine, 6-(4-methoxyphenyl)-N4,N4-bis(phenylmethyl)- (9CI) (CA INDEX NAME)



RN 278799-96-5 CAPLUS
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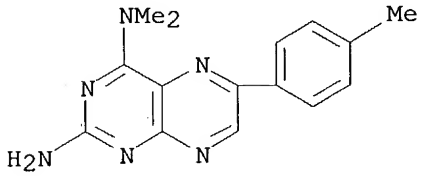

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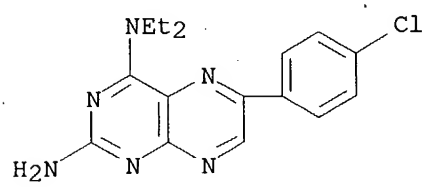
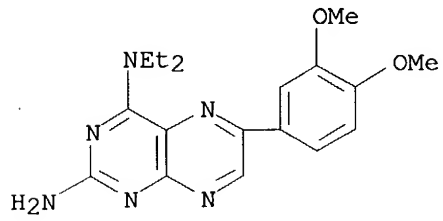
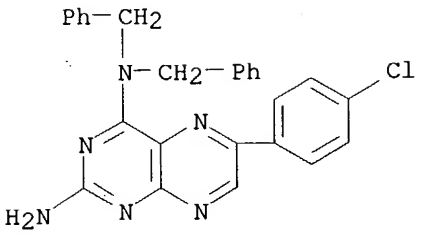


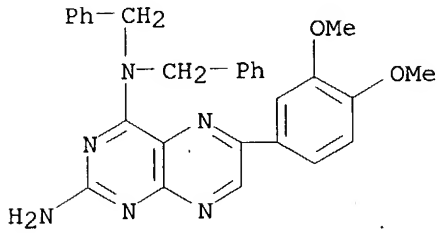
RN 278799-99-8 CAPLUS
CN 2,4-Pteridinediamine, 6-(3,4-dimethoxyphenyl)-N4,N4-diethyl- (9CI) (CA INDEX NAME)



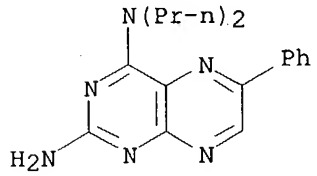
RN 278800-00-3 CAPLUS
CN 2,4-Pteridinediamine, 6-(4-chlorophenyl)-N4,N4-bis(phenylmethyl)- (9CI) (CA INDEX NAME)



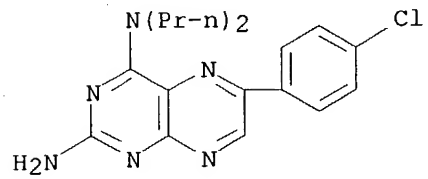
RN 278800-01-4 CAPLUS
CN 2,4-Pteridinediamine, 6-(3,4-dimethoxyphenyl)-N4,N4-bis(phenylmethyl)- (9CI) (CA INDEX NAME)



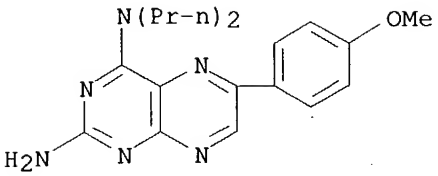
RN 278800-02-5 CAPLUS
CN 2,4-Pteridinediamine, 6-phenyl-N4,N4-dipropyl- (9CI) (CA INDEX NAME)



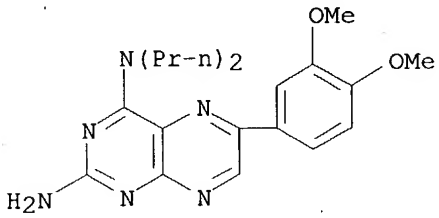
RN 278800-03-6 CAPLUS
CN 2,4-Pteridinediamine, 6-(4-chlorophenyl)-N4,N4-dipropyl- (9CI) (CA INDEX NAME)



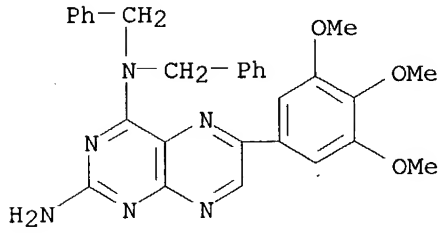
RN 278800-04-7 CAPLUS
CN 2,4-Pteridinediamine, 6-(4-methoxyphenyl)-N4,N4-dipropyl- (9CI) (CA INDEX NAME)



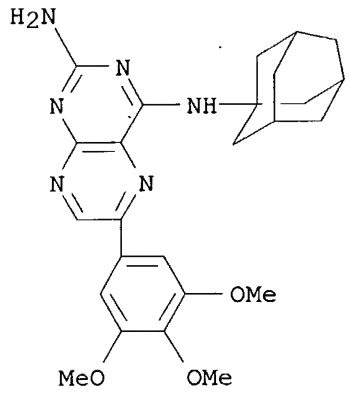
RN 278800-05-8 CAPLUS
CN 2,4-Pteridinediamine, 6-(3,4-dimethoxyphenyl)-N4,N4-dipropyl- (9CI) (CA INDEX NAME)



RN 278800-17-2 CAPLUS
CN 2,4-Pteridinediamine, N4,N4-bis(phenylmethyl)-6-(3,4,5-trimethoxyphenyl)- (9CI) (CA INDEX NAME)

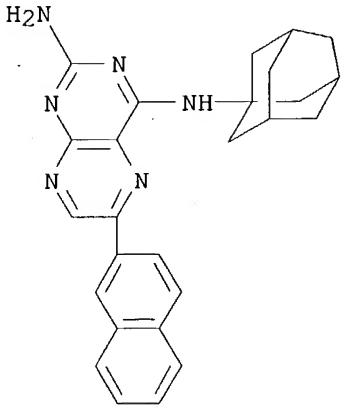


RN 278800-19-4 CAPLUS
CN 2,4-Pteridinediamine, N4-tricyclo[3.3.1.13,7]dec-1-yl-6-(3,4,5-trimethoxyphenyl)- (9CI) (CA INDEX NAME)

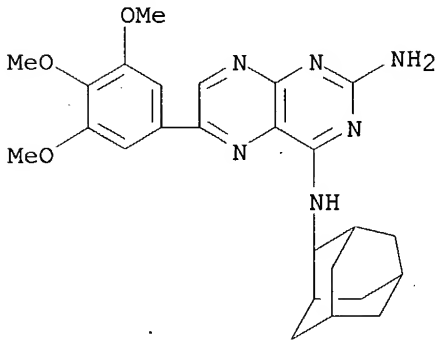


RN 278800-20-7 CAPLUS

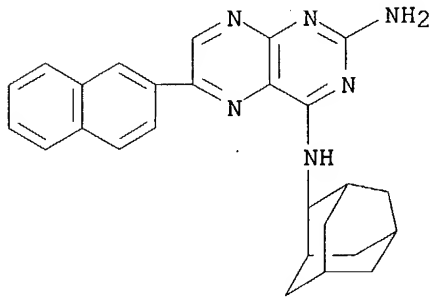
CN 2,4-Pteridinediamine, 6-(2-naphthalenyl)-N4-tricyclo[3.3.1.13,7]dec-1-yl- (9CI) (CA INDEX NAME)



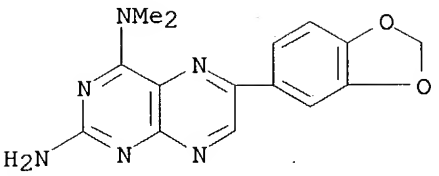
RN 278800-21-8 CAPLUS
CN 2,4-Pteridinediamine, N4-tricyclo[3.3.1.13,7]dec-2-yl-6-(3,4,5-trimethoxyphenyl)- (9CI) (CA INDEX NAME)



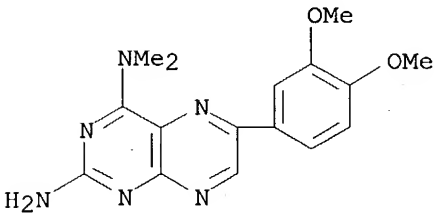
RN 278800-22-9 CAPLUS
CN 2,4-Pteridinediamine, 6-(2-naphthalenyl)-N4-tricyclo[3.3.1.13,7]dec-2-yl- (9CI) (CA INDEX NAME)



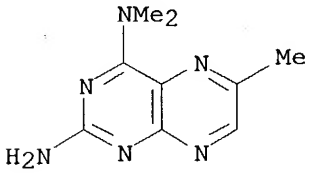
RN 278800-24-1 CAPLUS
CN 2,4-Pteridinediamine, 6-(1,3-benzodioxol-5-yl)-N4,N4-dimethyl- (9CI) (CA INDEX NAME)



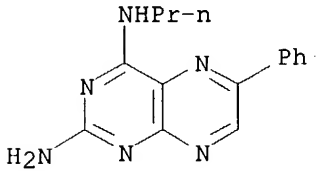
RN 278800-26-3 CAPLUS
CN 2,4-Pteridinediamine, 6-(3,4-dimethoxyphenyl)-N4,N4-dimethyl- (9CI) (CA INDEX NAME)



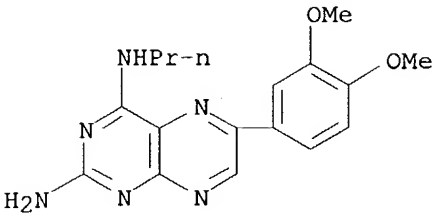
RN 278800-27-4 CAPLUS
CN 2,4-Pteridinediamine, N4,N4,6-trimethyl- (9CI) (CA INDEX NAME)



RN 278800-29-6 CAPLUS
CN 2,4-Pteridinediamine, 6-phenyl-N4-propyl- (9CI) (CA INDEX NAME)



RN 278800-30-9 CAPLUS
CN 2,4-Pteridinediamine, 6-(3,4-dimethoxyphenyl)-N4-propyl- (9CI) (CA INDEX NAME)



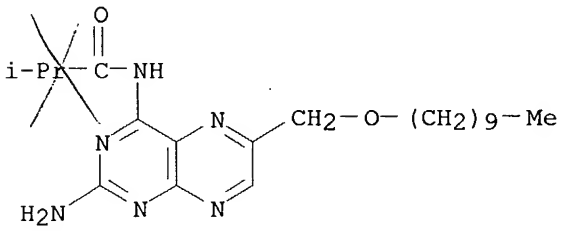
REFERENCE COUNT: 9 THERE ARE 9 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 4 OF 10 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1999:766098 CAPLUS
DOCUMENT NUMBER: 132:93157
TITLE: Pteridines CX. Synthesis and properties of 6-substituted 2,4-diaminopteridines and pterins
AUTHOR(S): Traub, Hermann; Pfleiderer, Wolfgang
CORPORATE SOURCE: Fakultat Fur Chemie, Universitat Konstanz, Konstanz, D-78432, Germany
SOURCE: Pteridines (1999), 10(3), 79-90
CODEN: PTRDEO; ISSN: 0933-4807
PUBLISHER: International Society of Pteridinology
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 132:93157

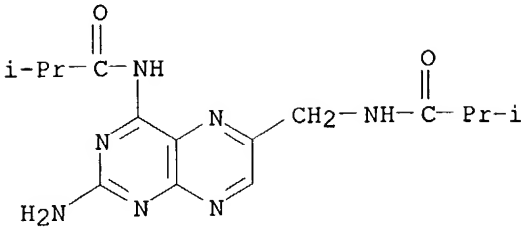
AB A series of 6-substituted 2,4-diaminopteridines and pterins were synthesized by nucleophilic displacement reactions at the side chain of 6-bromomethyl-2,4-diaminopteridine and 6-bromomethylpterin using various types of O-, N- and S-nucleophiles.

IT **254755-84-5P 254755-85-6P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(synthesis of 6-substituted 2,4-diaminopteridines and pterins via nucleophilic substitution reactions)

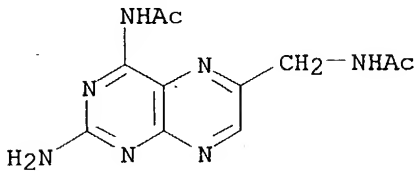
RN 254755-84-5 CAPLUS
CN Propanamide, N-[2-amino-6-[(decyloxy)methyl]-4-pteridinyl]-2-methyl- (9CI) (CA INDEX NAME)



RN 254755-85-6 CAPLUS
CN Propanamide, N-[2-amino-6-[[(2-methyl-1-oxopropyl)amino]methyl]-4-pteridinyl]-2-methyl- (9CI) (CA INDEX NAME)



IT **254755-86-7P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(synthesis of 6-substituted 2,4-diaminopteridines and pterins via nucleophilic substitution reactions)
RN 254755-86-7 CAPLUS
CN Acetamide, N-[[4-(acetylamino)-2-amino-6-pteridinyl]methyl]- (9CI) (CA INDEX NAME)



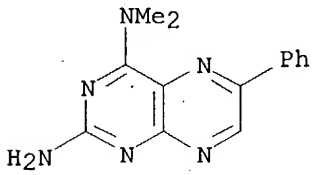
REFERENCE COUNT: 36 THERE ARE 36 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 5 OF 10 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1999:589097 CAPLUS
DOCUMENT NUMBER: 131:317316
TITLE: Inhibition of Neuronal Nitric Oxide Synthase by 4-Amino Pteridine Derivatives: Structure-Activity Relationship of Antagonists of (6R)-5,6,7,8-Tetrahydrobiopterin Cofactor
AUTHOR(S): Froehlich, Lothar G.; Kotsonis, Peter; Traub, Hermann; Taghavi-Moghadam, Shahriyar; Al-Masoudi, Najim; Hofmann, Heinrich; Strobel, Hartmut; Matter, Hans; Pfleiderer, Wolfgang; Schmidt, Harald H. H. W.
CORPORATE SOURCE: Department of Pharmacology and Toxicology, Julius-Maximilians University Wuerzburg, Wuerzburg, 97078, Germany
SOURCE: Journal of Medicinal Chemistry (1999), 42(20), 4108-4121
CODEN: JMCMAR; ISSN: 0022-2623
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The family of nitric oxide synthases (NOS) catalyzes the conversion of L-arginine to L-citrulline and nitric oxide (NO), an important cellular messenger mol. which has been implicated in the pathophysiol. of septic shock and inflammatory and neurodegenerative disease states. NOS can be maximally activated by the ubiquitous cofactor, (6R)-5,6,7,8-tetrahydrobiopterin (H4Bip), and antagonists of H4Bip may be of therapeutic importance to inhibit pathol. high NO formation. The 4-amino substituted analog of H4Bip was reported to be a potent NOS inhibitor. Therefore, we developed a series of novel 4-amino pteridine derivs., anti-pterins, to pharmacol. target the neuronal isoform of nitric oxide

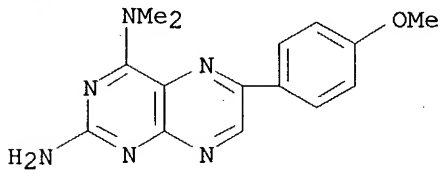
synthase (NOS-I). To functionally characterize the pterin/anti-pterin interaction and establish a structure-activity relationship (SAR), we systematically altered the substituents in the 2-, 4-, 5-, 6-, and 7-position of the pteridine nucleus. Varying the substitution pattern in the 2-, 5-, and 7-position resulted in no significant inhibitory effect on enzyme activity. In contrast, bulky substituents in the 6-position, such as Ph, markedly increased the inhibitory potency of the reduced 4-amino-5,6,7,8-tetrahydropteridines, possibly as a consequence of hydrophobic interactions within NOS-I. However, this was not the case for the aromatic 4-amino pteridines. Interestingly, chemical modification of the 4-amino substituent by dialkyl/diaralkylation together with 6-arylation of the aromatic 2,4-diamino pteridine resulted in potent and efficacious inhibitors of NOS-I, suggesting possible hydrophilic and hydrophobic interactions within NOS-I. This SAR agrees with (a) the recently published crystal structure of the oxygenase domain of the inducible NOS isoform (NOS-II) and (b) the comparative mol. field anal. of selected NOS-I inhibitors, which resulted in a 3D-QSAR model of the pterin binding site interactions. Further optimization should be possible when the full length structure of NOS-I becomes available.

IT **247913-51-5P 247913-52-6P 247913-54-8P**
247913-55-9P 247913-56-0P 247913-57-1P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PRP (Properties); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(synthesis of and inhibition of neuronal nitric oxide synthase by aminopteridines)

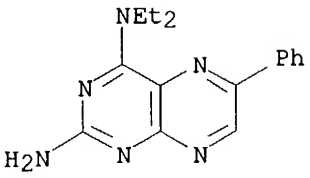
RN 247913-51-5 CAPLUS
CN 2,4-Pteridinediamine, N4,N4-dimethyl-6-phenyl- (9CI) (CA INDEX NAME)



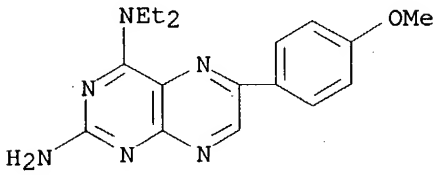
RN 247913-52-6 CAPLUS
CN 2,4-Pteridinediamine, 6-(4-methoxyphenyl)-N4,N4-dimethyl- (9CI) (CA INDEX NAME)



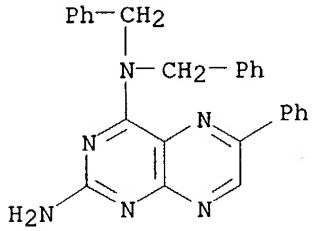
RN 247913-54-8 CAPLUS
CN 2,4-Pteridinediamine, N4,N4-diethyl-6-phenyl- (9CI) (CA INDEX NAME)



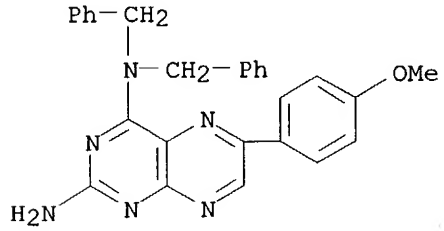
RN 247913-55-9 CAPLUS
CN 2,4-Pteridinediamine, N4,N4-diethyl-6-(4-methoxyphenyl)- (9CI) (CA INDEX NAME)



RN 247913-56-0 CAPLUS
CN 2,4-Pteridinediamine, 6-phenyl-N4,N4-bis(phenylmethyl)- (9CI) (CA INDEX NAME)



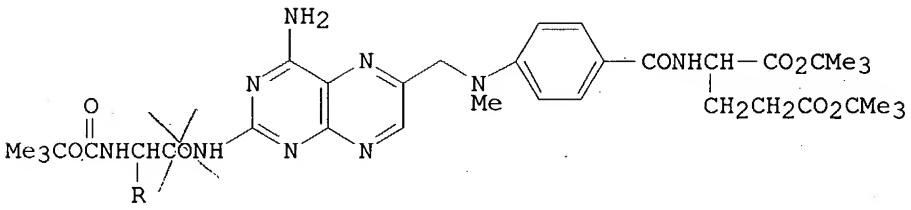
RN 247913-57-1 CAPLUS
CN 2,4-Pteridinediamine, 6-(4-methoxyphenyl)-N4,N4-bis(phenylmethyl)- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 60 THERE ARE 60 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 6 OF 10 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1993:7345 CAPLUS
DOCUMENT NUMBER: 118:7345
TITLE: Synthesis and properties of N-(α-aminoacyl) derivatives of methotrexate
AUTHOR(S): Cheung, H. T. A.; Dong, Z.; Smal, M.; Tattersall, M.

H. N.
CORPORATE SOURCE: Dep. Pharm., Univ. Sydney, Sydney, 2006, Australia
SOURCE: Pteridines (1992), 3(1-2), 101-2
CODEN: PTRDEO; ISSN: 0933-4807
DOCUMENT TYPE: Journal
LANGUAGE: English
GI



I

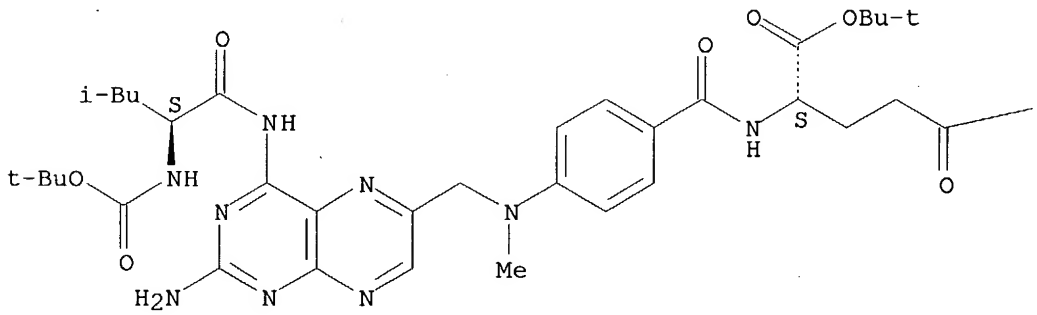
AB Methotrexate was converted to its di-tert-Bu ester which coupled with Boc-α-amino acids (leucine, isoleucine, norleucine) to give the 2-(N-Boc-α-aminoacyl) derivs. I (R = CH2CHMe2, CHMeEt, n-Bu) along with the 4-(N-Boc-α-aminoacyl) and 2,4-di(N-Boc-α-aminoacyl) derivs. I were treated with F3CCO2H to give the corresponding deprotected 2-α-aminoacylmethotrexates in quant. yields.

IT **125507-12-2P 144864-86-8P 144864-87-9P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of)

RN 125507-12-2 CAPLUS
CN L-Glutamic acid, N-[4-[[[2-amino-4-[[2-[[(1,1-dimethylethoxy)carbonyl]amino]-4-methyl-1-oxopentyl]amino]-6-pteridinyl]methyl]methylamino]benzoyl]-, bis(1,1-dimethylethyl) ester, (S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



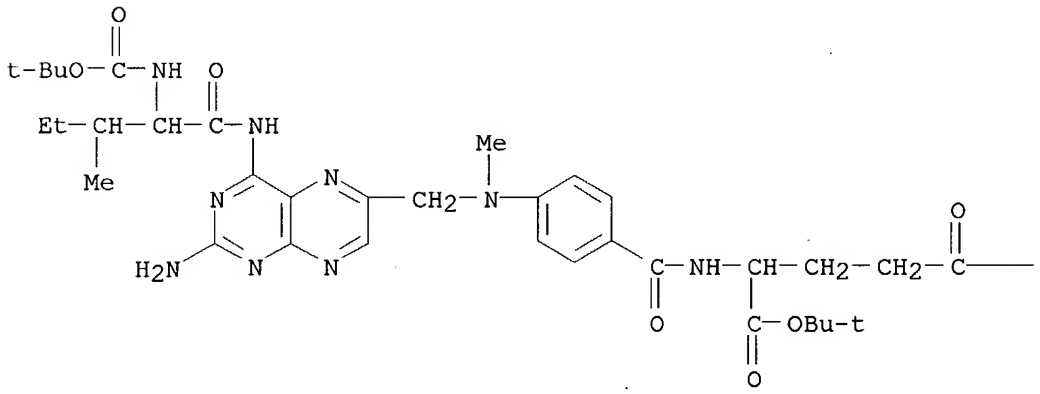
PAGE 1-B

—OBu-t

RN 144864-86-8 CAPLUS
CN L-Glutamic acid, N-[4-[[[2-amino-4-[[2-[[(1,1-

dimethylethoxy)carbonyl]amino]-3-methyl-1-oxopentyl]amino]-6-pteridinyl]methyl]methylamino]benzoyl]-, bis(1,1-dimethylethyl) ester, [S-(R*,R*)]- (9CI) (CA INDEX NAME)

PAGE 1-A



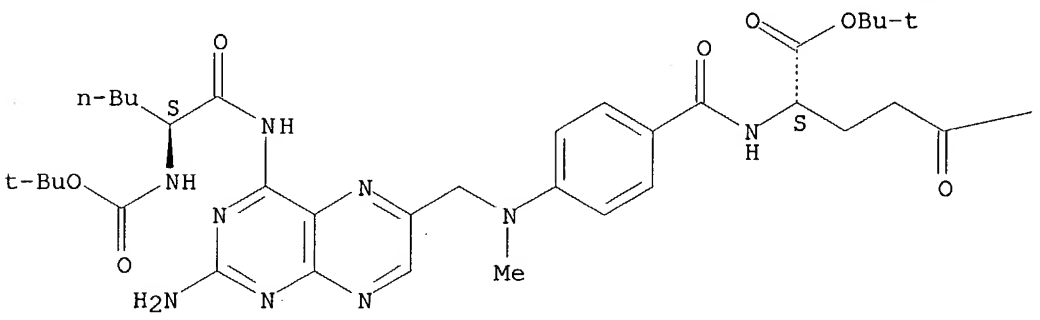
PAGE 1-B

—OBu-t

RN 144864-87-9 CAPLUS
CN L-Glutamic acid, N-[4-[[[2-amino-4-[[2-[[(1,1-dimethylethoxy)carbonyl]amino]-1-oxohexyl]amino]-6-pteridinyl]methyl]methylamino]benzoyl]-, bis(1,1-dimethylethyl) ester, (S)- (9CI) (CA INDEX NAME)

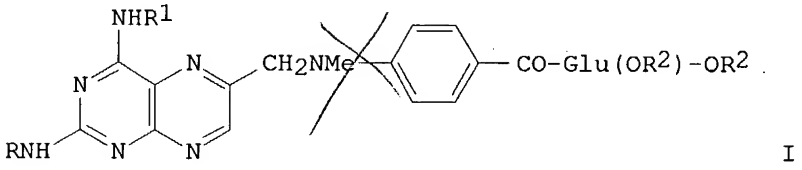
Absolute stereochemistry.

PAGE 1-A



—OBu-t

L8 ANSWER 7 OF 10 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1990:99224 CAPLUS
DOCUMENT NUMBER: 112:99224
TITLE: N-(L-α-aminoacyl) derivatives of methotrexate
AUTHOR(S): Cheung, H. T. Andrew; Boadle, Deborah K.; Tran, Trung Q.
CORPORATE SOURCE: Dep. Pharm., Univ. Sydney, Sydney, Australia
SOURCE: Heterocycles (1989), 28(2), 751-8
CODEN: HTCYAM; ISSN: 0385-5414
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 112:99224
GI



I

AB Coupling of methotrexate ester I (R = R1 = H, R2 = CMe3) with alanine and leucine derivs. gave aminoacyl analogs I (R, R1 = Boc-Leu, Boc-Ala; R2 = CMe3; Boc = Me3CO2C). The positions of the aminoacyl groups were determined by 13C NMR. Hydrolysis of I (R = Boc-Ala, Boc-Leu; R1 = H, R2 = Me3C) gave methotrexate analogs I (R = H-Ala, H-Leu; R1 = R2 = H) (II), but the other aminoacyl analogs gave decomposition products. Enzymic cleavage of II gave methotrexate.

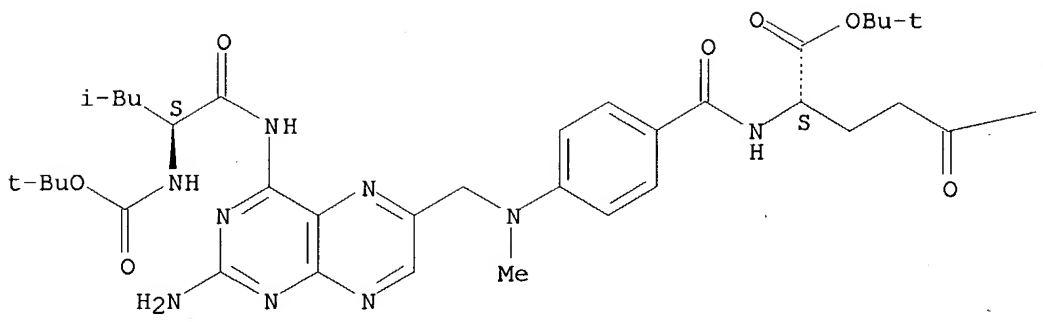
IT **125507-12-2P 125507-13-3P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation, attempted deblocking, and carbon-13 NMR of)

RN 125507-12-2 CAPLUS

CN L-Glutamic acid, N-[4-[[[2-amino-4-[[2-[[(1,1-dimethylethoxy)carbonyl]amino]-4-methyl-1-oxopentyl]amino]-6-pteridinyl]methyl]methylamino]benzoyl]-, bis(1,1-dimethylethyl) ester, (S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



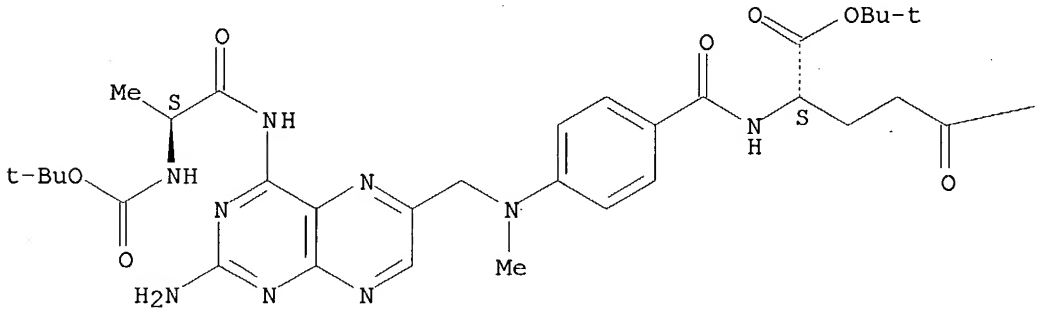
PAGE 1-B

—OBu-t

RN 125507-13-3 CAPLUS
CN L-Glutamic acid, N-[4-[[[2-amino-4-[[2-[[(1,1-dimethylethoxy)carbonyl]amino]-1-oxopropyl]amino]-6-pteridinyl]methyl]methylamino]benzoyl]-, bis(1,1-dimethylethyl) ester, (S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A

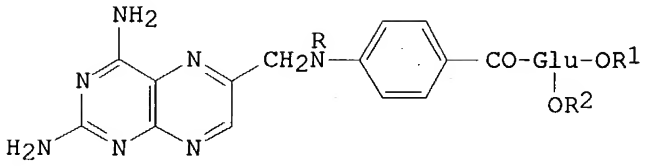


PAGE 1-B

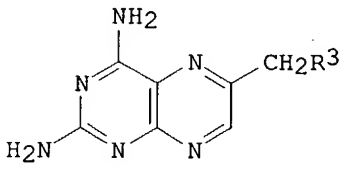
—OBu-t

L8 ANSWER 8 OF 10 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1985:167139 CAPLUS
DOCUMENT NUMBER: 102:167139
TITLE: Methotrexate analogs. 25. Chemical and biological studies on the γ-tert-butyl esters of methotrexate and aminopterin
AUTHOR(S): Rosowsky, Andre; Freisheim, James H.; Bader, Henry;

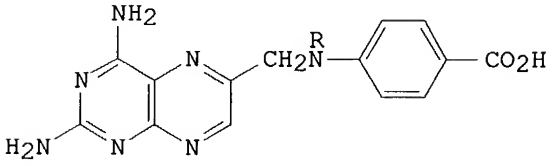
Forsch, Ronald A.; Susten, Sandra A.; Cucchi, Carol A.; Frei, Emil, III
CORPORATE SOURCE: Dana-Farber Cancer Inst., Harvard Med. Sch., Boston, MA, 02115, USA
SOURCE: Journal of Medicinal Chemistry (1985), 28(5), 660-7
CODEN: JMCMAR; ISSN: 0022-2623
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 102:167139
GI



I



IV



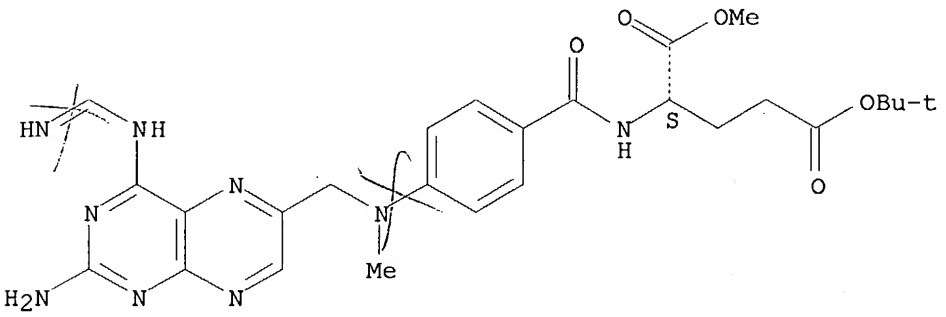
V

AB γ-tert-Bu aminopterin (I; R = R1 = H, R2 = CMe3) (II) was prepared, and new routes to the known γ-tert-Bu methotrexate (I; R = Me, R1 = H, R2 = CMe3) (III) were developed. Thus, pteridine IV (R3 = OH) was brominated by Br2/PPh3 to give IV (R3 = Br), which was treated in situ with p-H2NC6H4CO2H to give pteroic acid V (R = H), which was formylated to give V (R = CHO). The latter was condensed with H-Glu(OCMe3)-OMe.HCl by ClCO2CH2CHMe2 in DMF containing Et3N to give I (R = CHO, R1 = Me, R2 = CMe3), which was hydrolyzed and then deformylated to give II. II was also prepared by treating IV.HBr (R3 = Br) with p-RNHC6H4CO-Glu(OCMe3)-OR1 (VI, R = R1 = H) in AcNMe2 containing Me2CHNEt2. III was prepared by brominating IV (R3 = OH), treating the resulting IV (R3 = Br) with VI (R = R1 = Me), and hydrolyzing the resulting I (R = R1 Me, R2 = CMe3). The inhibitory effects of II on the activity of dihydrofolate reductase (DHFR) from L1210 murine leukemia cells, the growth of 4210 cells and CEM human leukemic lymphoblasts in suspension culture, and the growth of human squamous cell carcinoma of the head and neck in monolayer culture were compared with the effects of III and the parent acids aminopterin (I, R-R2 = H) and methotrexate (I, R = Me, R1 = R2 = H). The activity of II was close to that of III in the DHFR inhibition assay, but II was more potent than III against cells in culture and against L1210 leukemia in mice.

IT **95485-11-3P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

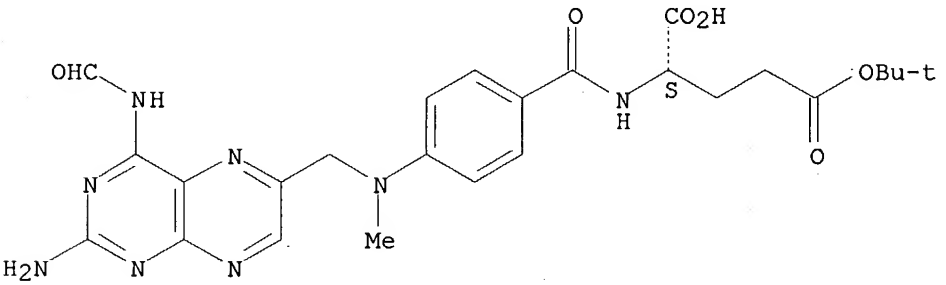
(preparation and hydrolysis of)
RN 95485-11-3 CAPLUS
CN L-Glutamic acid, N-[4-[[[2-amino-4-[(iminomethyl)amino]-6-pteridinyl]methyl]methylamino]benzoyl]-, 5-(1,1-dimethylethyl) 1-methyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



IT **95485-13-5P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of)
RN 95485-13-5 CAPLUS
CN L-Glutamic acid, N-[4-[[[2-amino-4-(formylamino)-6-pteridinyl]methyl]methylamino]benzoyl]-, 5-(1,1-dimethylethyl) ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



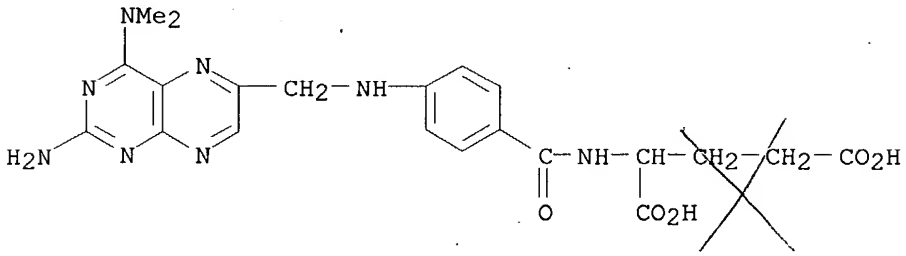
L8 ANSWER 9 OF 10 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1961:28447 CAPLUS
DOCUMENT NUMBER: 55:28447
ORIGINAL REFERENCE NO.: 55:5650f-g
TITLE: A simple method for the demonstration of antimetabolites
AUTHOR(S): Pershin, G. N.; Shcherbakova, L. I.
CORPORATE SOURCE: S. Ordzhonikidze All-Union Sci.-Research Chemo-Pharm. Inst., Moscow
SOURCE: Biokhimiya (Moscow) (1960), 25, 684-7
CODEN: BIOHAO; ISSN: 0320-9725
DOCUMENT TYPE: Journal
LANGUAGE: Unavailable
AB Antimetabolites, such as 6-mercaptopurine, 2-amino-6-mercaptopurine and 8-azaguanine, which interfered with purine metabolism, arrested the growth of Escherichia coli; antimetabolite activity was counteracted by

hypoxanthine, adenine, and guanine. Among the other substances normally used in arresting malignant growths, aminopterin, 4-dimethylaminopteroyglutamic acid, and embichin also arrested E. coli growth. Purine bases had no effect on these substances. Colchamine and thiophosphoramide (thioteph) arrested the growth of E. coli in high concns. only; Myleran was ineffective.

IT **103508-85-6**, Glutamic acid, N-{p-{[(2-amino-4-dimethylamino-6-pteridinyl)methyl]amino}benzoyl}-
(effect on Escherichia coli)

RN 103508-85-6 CAPLUS

CN Glutamic acid, N-[p-[[(2-amino-4-dimethylamino-6-pteridinyl)methyl]amino]benzoyl]- (6CI) (CA INDEX NAME)



L8 ANSWER 10 OF 10 CAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 1961:9549 CAPLUS

DOCUMENT NUMBER: 55:9549

ORIGINAL REFERENCE NO.: 55:1909c

TITLE: Evaluation of antileukemic agents employing advanced leukemia L1210 in mice. III. Congeners of folic acid

AUTHOR(S): Venditti, John M.; Humphreys, Stewart R.; Mantel, Nathan; Kline, Ira; Goldin, Abraham

CORPORATE SOURCE: Natl. Cancer Inst., Bethesda, MD

SOURCE: Cancer Research (1960), 20(No. 10;Pt. 2), 698-733
CODEN: CNREA8; ISSN: 0008-5472

DOCUMENT TYPE: Journal

LANGUAGE: Unavailable

AB Unavailable

IT **97115-74-7**, Glutamic acid, N-{p-{[(2-amino-4-dimethylamino-6-pteridinyl)methyl]methylamino}benzoyl}-
(as neoplasm inhibitor)

RN 97115-74-7 CAPLUS

CN Glutamic acid, N-[p-[[[2-amino-4-(dimethylamino)-6-pteridinyl]methyl]methylamino]benzoyl]- (6CI, 7CI) (CA INDEX NAME)